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TITLE: LIMITED TOXICITY AND MUTAGENICITY TESTING OF FIVE UNICHARGE PROPELLANT COMPOUNDS

SUBTITLE: Evaluation of Five Unicharge Propellants in the Acute Exposure Dermal Toxicity

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N-methyl-,n-ethyl- and n-butyl-2nitratoethyl nitramine (MeNENA, EtNENA and BuNENA) and bis (2,2-dinitropropyl) acetal/formal (~50/50 mixture) ± diphenyl amine stabilizer (BDNPA/F±DPA) were tested for dermal toxicity. One group of ten rabbits per study received the test article once by topical application and was held in contact with the skin for 24 hours. Animals were observed for clinical signs and mortality daily for 14 days. One animal receiving BDNPA/F-DPA died during the study. No mortality was observed in any other treatment groups. Based upon the results of these assays, the estimated acute dermal LD_{50} for MeNENA, EtNENA, BuNENA and BDNPA/F±DPA, was determined to be greater than 2000 mg/kg.

14. SUBJECT TERMS

Dermal toxicity, unicharge, propellants, methyl-NENA, ethyl-NENA, butyl-NENA, bis-(2,2-dinitropropyl) acetal bis-(2,2-dinitropropyl)formal, lab animals, RAIII

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Evaluation of Five Unicharge Propellants in the
Acute Exposure Dermal Toxicity

EXECUTIVE SUMMARY

In Dermal Limit Tests, one group of ten (10) rabbits (five males and five females) per study was exposed to the test article at 2000 mg/kg. Animals were observed for clinical signs and mortality once daily for fourteen days.

Clinical signs observed in the bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated animals included decreased activity, decreased muscle tone, abnormal gait, abnormal stance, diarrhea and dyspnea. No clinical signs were observed in any animal receiving n-methyl-2-nitratoethyl nitramine, n-ethyl-2-nitratoethyl nitramine, n-butyl-2-nitratoethyl nitramine and bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer. With the exception of a slight decrease in mean body weight on Day 7 in the n-methyl-2-nitratoethyl nitramine females, there were no apparent effects on mean body weight throughout any other treatment group. One of ten rabbits died in the bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated group. None of the animals died in any of the other treatment groups. Necropsy of the animal that died during the study revealed a red, distended cecum and distended intestines. Terminal necropsy revealed distended intestines and stomach in animals administered bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer and pale and enlarged kidneys, enlarged spleen and ascites in bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated animals. No visible lesions were observed in any other animal in any treatment group at terminal necropsy.

Based upon the observations made in the Acute Exposure Dermal Toxicity studies in rabbits, the estimated acute dermal LD_{50} (combined sexes) for n-methyl-2-nitratoethyl nitramine, n-ethyl-2-nitratoethyl nitramine, n-butyl-2-nitratoethyl nitramine and bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer and bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer was determined to be greater than 2000 mg/kg.

Evaluation of Five Unicharge Propellants
in the Acute Exposure Dermal Toxicity

PH 422-US-001...005-91

STUDY DESCRIPTION

Sponsor:	U.S. Army Medical Research and Development Laboratory Fort Detrick Frederick, MD 21702-5010
Testing Facility:	Pharmakon Research International, Inc. P.O. Box 609 Waverly, PA 18471
Test Facility Study Conduct S.O.P. No.:	PH-422
Study Numbers:	PH 422-US-001-91 PH 422-US-002-91 PH 422-US-003-91 PH 422-US-004-91 PH 422-US-005-91
Purpose of the Study:	To evaluate the dermal toxicity of the test article when administered to rabbits at 2000 mg/kg.
Ownership of the Study:	The sponsor owns the study. All raw data, analysis and reports are the property of the sponsor.
Study Monitor:	Major Nathaniel Powell, U.S. Army Medical Research and Development Laboratory
Study Director:	Victor T. Mallory, B.S., RLAT, Pharmakon Research International, Inc.
Technical Performance:	Susan E. Armondi, LAT, Thomas O'Neill, B.S., LAT, Kim DiLeo, B.S., LAT, Maura J. Bieszczad and Shirley Chappuis, A.S., AVT, LAT
Q.A.U. Responsible Personnel:	Leslie J. Pinnell, M.S.
Date Study Director Signed Protocols:	September 23, 1991

Evaluation of Five Unicharge Propellants
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Dates of Technical Performance:	**PH 422-US-002-91** - November 15, 1991 through November 29, 1991 **PH 422-US-003-91** - November 15, 1991 through November 29, 1991 **PH 422-US-001-91** - December 4, 1991 through December 18, 1991 **PH 422-US-004-91** - December 6, 1991 through December 20, 1991 **PH 422-US-005-91** - December 10, 1991 through December 24, 1991
Good Laboratory Practices Statement:	These studies were conducted in compliance with the Good Laboratory Practices Regulations. There were no deviations from the GLP Regulations which affected the quality or integrity of the study. Q.A.U. findings from the inspections conducted of this study and from the audit of the final report are documented and have been provided to the study director and the test facility management.
Records Maintained:	All raw data, final report documentation and protocol will be maintained in the archives of Pharmakon Research International, Inc.
Recordings:	Standard Pharmakon Notebook
Notebook Reference:	Notebook #1539, pages 116-118, 120-122, 227-229, 253-255, 260-262

TEST ARTICLES

TEST ARTICLE	DESCRIPTION	LOT #	CAS #	DATE(S) SUBMITTED
n-methyl-2-nitratoethyl nitramine (MeNENA)	white solid	XAP-MeNENA	17096-47-8	9/19/91
n-ethyl-2-nitratoethyl nitramine (EtNENA)	yellow liquid	XAP-EtNENA-4B	85068-73-1	9/19/91
n-butyl-2-nitratoethyl nitramine (BuNENA)	yellow liquid	XAP-BuNENA-15B	82486-82-6	9/19/91

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TEST ARTICLE	DESCRIP-TION	LOT #	CAS #	DATE(S) SUBMITTED
bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer (BDNPA/F+DPA)	yellow liquid	Set #1 87	5108-69-0	9/19/91 12/5/91
bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer (BDNPA/F-DPA)	yellow liquid	Set #2 87	5917-61-3	9/19/91 12/5/91

Analysis of Purity: The purity, identity, strength and stability of the test articles were the responsibility of the sponsor.

Stability: There was no apparent change in the physical appearance of the test articles during administration.

TEST SYSTEM

Species: Rabbit

Strain: New Zealand White

Suppliers (Sources): CAMM Research Lab Animals, Wayne, NJ
Hazleton Research Products, Denver, PA
Buckshire Corporation, Perkasie, PA

Sex: Male and female

Age at Initiation: 8-12 weeks

Weight Range: 1.814 to 3.188 kilograms

No. on Study: Ten (10) (five males and five females) per study

Method and Justification for Randomization: Randomly assigned to study by health status

Acclimation Period: Minimum of five (5) days

System of Identification: Cage cards were marked with the study number, animal number, dose level and sex. Rabbits were ear tagged.

HUSBANDRY

Research Facility Registration: U.S.D.A. Registration No. 23-R-107 under the Animal Welfare Act 74: SC 2131 et seq.

Animal Rooms: Separate isolation by test system
Light cycle - 12 hours light, 12 hours dark
Temperature/Relative Humidity - Every attempt was made to maintain a temperature of 20°C ± 3°C (63-73°F) and a relative humidity of 30 to 70%.

Any excursions outside the temperature or humidity ranges were of small magnitude and/or brief duration and did not adversely affect the validity of the study.

Housing: Rabbits were housed individually in cages sized in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council.

Sanitization: Waste material was removed twice weekly. Cages and feeders were sanitized every two weeks.

Food: Purina Lab Rabbit Chow H.F^{R}, ad libitum, food was checked daily and added or replaced as needed. Feeders are designed to reduce soiling, bridging and scattering.

Food Analysis: There were no contaminants that were reasonably expected to be present in the dietary material known to be capable of interfering with the purpose or conduct of the study.

Water: Fresh tap water, ad libitum.

Water Analysis: Water is monitored for contaminants at periodic intervals according to Standard Operating Procedure PH-018.

METHODS

Rationale for Test System: The albino rabbit is preferred because of its size, skin permeability and extensive database.

Evaluation of Five Unicharge Propellants
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Compound Preparation:	All test articles were dosed as received from the sponsor with the exception of 1-methyl-2-nitratoethyl nitramine. 1-Methyl-2-nitratoethyl nitramine was placed in a desiccator approximately 24 hours prior to administration.
Dose Administration:	2000 mg/kg
Rationale for Dose Selection:	As required by the regulatory agencies.
Route of Administration:	The test material was applied directly on intact skin sites.
Rationale for Route of Administration:	The study is designed specifically for the assessment of dermal absorption and resultant toxicity.
Frequency of Administration:	Once (1) per test article
No. of Animals Per Dose Group:	Ten (10)
Length of Studies:	Fourteen (14) days
Method of Study Performance:	Approximately 24 hours before testing, fur was clipped from the dorsal area of the trunk of the test animals. The test article was applied directly onto the exposed intact skin of the animals taking care to spread the substance evenly over the entire area. A square gauze patch was placed on the animals to cover the dosed area. The animals were wrapped with rubber dam and an elastic bandage to retard evaporation. The test article was held in contact with the skin for twenty-four hours. Following the twenty-four hour period of exposure, the wrappings were removed and the skin sites were wiped with water and gauze or acetone and gauze (n-methyl-2-nitratoethyl nitramine) to remove any residual test article. Observations were recorded daily through Day 14. Body weights were recorded at initiation and on Days 7 and 14. All rabbits were sacrificed by a lethal injection on Day 14 and a gross necropsy was performed.

RESULTS

Clinical signs observed in the bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated animals included decreased activity, decreased muscle tone, abnormal gait, abnormal stance, diarrhea and dyspnea. No clinical signs were observed in any animal receiving n-methyl-2 nitratoethyl nitramine, n-ethyl-2 nitratoethyl nitramine, n-butyl-2 nitratoethyl nitramine and bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer. One of ten rabbits died in the bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated group. None of the animals died in any of the other treatment groups. Necropsy of the animal that died during the study revealed a red, distended cecum and distended intestines. Terminal necropsy revealed distended intestines and stomach in animals administered bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer and pale, enlarged kidneys, enlarged spleen and ascites in bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated animals. No visible lesions were observed in any other animal in any treatment group at terminal necropsy.

CONCLUSION

Based upon the observations made in the Acute Exposure Dermal Toxicity studies in rabbits, the estimated acute dermal LD_{50} (combined sexes) for n-methyl-2 nitratoethyl nitramine, n-ethyl-2 nitratoethyl nitramine, n-butyl-2 nitratoethyl nitramine, bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer and bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer was determined to be greater than 2000 mg/kg.

Table I

Summary of Clinical Observations of Five Unicharge Propellants
in the Acute Exposure Dermal Toxicity

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N-Methyl-2 Nitratoethyl Nitramine

Clinical Signs	Sex	Hours 24	Days 2	3	4	5	6	7	8	9	10	11	12	13	14
No signs	M	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	F	5	5	5	5	5	5	5	5	5	5	5	5	5	5

N-Ethyl-2 Nitratoethyl Nitramine

Clinical Signs	Sex	Hours 24	Days 2	3	4	5	6	7	8	9	10	11	12	13	14
No signs	M	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	F	5	5	5	5	5	5	5	5	5	5	5	5	5	5

N-Butyl-2 Nitratoethyl Nitramine

Clinical Signs	Sex	Hours 24	Days 2	3	4	5	6	7	8	9	10	11	12	13	14
No signs	M	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	F	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Table I (continued)

Summary of Clinical Observations of Five Unicharge Propellants
in the Acute Exposure Dermal Toxicity

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Bis-(2,2-Dinitropropyl) Acetal with Diphenyl Amine Stabilizer

Clinical Signs	Sex	Hours 24	Days 2	3	4	5	6	7	8	9	10	11	12	13	14
No signs	M	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	F	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Bis-(2,2-Dinitropropyl) Formal without Diphenyl Amine Stabilizer

Clinical Signs	Sex	Hours 24	Days 2	3	4	5	6	7	8	9	10	11	12	13	14
No signs	M	5	5	5	5	5	5	5	5	5	5	5	5	5	4
	F	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Decreased activity	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	1	1	1	1	0	0	0	0	0	0	0	0	0	0
Diarrhea	M	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	F	1	1	1	1	0	0	0	0	0	0	0	0	0	0
Decreased muscle tone	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Abnormal gait	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	0	1	1	1	0	0	0	0	0	0	0	0	0	0
Abnormal stance	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	0	1	1	1	0	0	0	0	0	0	0	0	0	0
Dyspnea	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	0	0	1	1	0	0	0	0	0	0	0	0	0	0

Table II

Summary of Mortality of Five Unicharge Propellants
in the Acute Exposure Dermal Toxicity

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N-Methyl-2 Nitratoethyl Nitramine

Dose (mg/kg)	Sex	No. of Rabbits	Days													Total Mortality
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2000	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
2000	F	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

N-Ethyl-2 Nitratoethyl Nitramine

Dose (mg/kg)	Sex	No. of Rabbits	Days													Total Mortality
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2000	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
2000	F	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

N-Butyl-2 Nitratoethyl Nitramine

Dose (mg/kg)	Sex	No. of Rabbits	Days													Total Mortality
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2000	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
2000	F	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

Table II (continued)

Summary of Mortality of Five Unicharge Propellants
in the Acute Exposure Dermal Toxicity

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Bis-(2,2-Dinitropropyl) Acetal with Diphenyl Amine Stabilizer

Dose (mg/kg)	Sex	No. of Rabbits	Days													Total Mortality
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2000	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
2000	F	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

Bis-(2,2-Dinitropropyl) Formal without Diphenyl Amine Stabilizer

Dose (mg/kg)	Sex	No. of Rabbits	Days													Total Mortality
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2000	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
2000	F	5	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1/5

Table III. Summary of Body Weights (g) of Five Unicharge Propellants in the Acute Exposure Dermal Toxicity

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N-Methyl-2 Nitratoethyl Nitramine

Animal Number	Sex	Initial	Day 7	Final
5521	M	2238	2244	2375
5522	M	2018	1932	1997
5523	M	2130	2098	2395
5524	M	1984	2046	2140
5525	M	1990	2073	2086
$\bar{x}$		2072.0	2078.6	2198.6
S.D.		109.89	112.16	177.80
N		5	5	5
5526	F	2158	2115	2346
5527	F	1935	1967	2278
5528	F	2007	1948	2234
5529	F	2000	1928	2023
5530	F	1991	1801	1935
$\bar{x}$		2018.2	1951.8	2163.2
S.D.		83.16	112.01	175.60
N		5	5	5

N-Ethyl-2 Nitratoethyl Nitramine

Animal Number	Sex	Initial	Day 7	Final
5271	M	2034	2186	2327
5272	M	2138	2192	2309
5273	M	2361	2521	2681
5274	M	1911	2137	2278
5275	M	1814	1934	2095
$\bar{x}$		2051.6	2194.0	2338.0
S.D.		211.97	210.86	212.87
N		5	5	5
5276	F	2340	2503	2613
5277	F	1866	1990	2084
5278	F	2444	2636	2755
5279	F	1865	1984	2115
5280	F	2160	2284	2396
$\bar{x}$		2135.0	2279.4	2392.6
S.D.		266.17	295.04	296.74
N		5	5	5

Table III. (cont'd) Summary of Body Weights (g) of Five Unicharge Propellants in the Acute Exposure Dermal Toxicity

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N-Butyl-2 Nitratoethyl Nitramine

Animal Number	Sex	Initial	Day 7	Final
5281	M	2092	2303	2563
5282	M	2180	2302	2509
5283	M	2182	2347	2602
5284	M	1876	2117	2408
5285	M	1819	2066	2289
$\bar{x}$		2029.8	2227.0	2474.2
S.D.		171.53	126.32	126.60
N		5	5	5
5286	F	2181	2381	2631
5287	F	1990	2114	2250
5288	F	2150	2326	2489
5289	F	2051	2301	2500
5290	F	1900	2029	2166
$\bar{x}$		2054.4	2230.2	2407.2
S.D.		115.29	150.76	192.54
N		5	5	5

Bis-(2,2-Dinitropropyl) Acetal with Diphenyl Amine Stabilizer

Animal Number	Sex	Initial	Day 7	Final
5541	M	2461	2522	2566
5542	M	3188	3438	3656
5543	M	3020	3186	3217
5544	M	2889	3064	3072
5545	M	2708	2873	3059
$\bar{x}$		2853.2	3016.6	3114.0
S.D.		281.11	344.16	390.34
N		5	5	5
5546	F	2839	3002	3107
5547	F	2108	2228	2415
5548	F	2830	3030	3165
5549	F	2634	2824	3029
5550	F	2758	2907	3095
$\bar{x}$		2633.8	2798.2	2962.2
S.D.		305.16	328.97	309.69
N		5	5	5

Table III. (cont'd) Summary of Body Weights (g) of Five Unicharge Propellants in the Acute Exposure Dermal Toxicity

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Bis-(2,2-Dinitropropyl) Formal without Diphenyl Amine Stabilizer

Animal Number	Sex	Initial	Day 7	Final
5531	M	2177	2431	2392
5532	M	2315	2483	2575
5533	M	2195	2309	2421
5534	M	2516	2655	2782
5535	M	2301	2494	2616
$\bar{x}$		2300.8	2474.4	2557.2
S.D.		135.12	124.82	158.23
N		5	5	5
5586	F	2241	2393	2521
5587	F	2012	2258	2396
5588	F	2207	2375	2500
5589	F	2335	2442	2448
5590	F	2051	-	-
$\bar{x}$		2169.2	2367.0	2466.3
S.D.		134.87	77.99	55.99
N		5	4	4

Table IV

Necropsy Observations (Incidence Values) of Five Unicharge Propellants in the Acute Exposure Dermal Toxicity

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N-Methyl-2 Nitratoethyl Nitramine

Observation	Interim Death Incidence		Terminal Necropsy Incidence	
	M	F	M	F
No visible lesions	-	-	5	5

N-Ethyl-2 Nitratoethyl Nitramine

Observation	Interim Death Incidence		Terminal Necropsy Incidence	
	M	F	M	F
No visible lesions	-	-	5	5

N-Butyl-2 Nitratoethyl Nitramine

Observation	Interim Death Incidence		Terminal Necropsy Incidence	
	M	F	M	F
No visible lesions	-	-	5	5

- Not applicable

Table IV (continued)

Necropsy Observations (Incidence Values) of Five Unicharge Propellants in the Acute Exposure Dermal Toxicity

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Bis-(2,2-Dinitropropyl) Acetal with Diphenyl Amine Stabilizer

Observation	Interim Death Incidence		Terminal Necropsy Incidence	
	M	F	M	F
No visible lesions	-	-	2	4
Stomach distended	-	-	1	0
Intestines distended	-	-	3	1

Bis-(2,2-Dinitropropyl) Formal without Diphenyl Amine Stabilizer

Observation	Interim Death Incidence		Terminal Necropsy Incidence	
	M	F	M	F
No visible lesions	-	0	5	3
Cecum				
distended	-	1	0	0
red	-	1	0	0
Intestines				
distended	-	1	0	0
Kidneys				
pale	-	0	0	1
enlarged	-	0	0	1
Spleen				
enlarged	-	0	0	1
Ascites	-	0	0	1

- Not applicable

QUALITY ASSURANCE UNIT STATEMENT

Study Nos.: PH 422-US-001-91
PH 422-US-002-91
PH 422-US-003-91
PH 422-US-004-91
PH 422-US-005-91

Study Director: Victor T. Mallory

The Quality Assurance Unit conducted the inspections listed below and reported the results to the study director and to management on the dates indicated.

The following inspections were performed:

Interval	Date
In Life Phase	12/4/91, 11/15/91, 11/15/91 12/6/91, 12/10/91
Necropsy Phase	12/18/91, 12/20/91
Reporting Phase	1/28/92

Date QAU Report Issued

To Study Director	To Management
1/28/92	1/28/92

Leslie J. Sunnell
Quality Assurance

1-28-92
Date

COMPLIANCE STATEMENT

This study was conducted in compliance with the Principles of Good Laboratory Practices (GLP) as promulgated by the following regulatory agencies:

EPA as stated in the Federal Register, 40 CFR Parts 160 and 792.

Organization for Economic Co-operation and Development Guidelines for Testing Chemicals (OECD), ISBN 92-64-12221-4, adopted by the council at its 535th meeting on May 12, 1981.

U.S. Food and Drug Administration as stated in 58 CFR Part 21.

Study Nos.: PH 422-US-001-91
PH 422-US-002-91
PH 422-US-003-91
PH 422-US-004-91
PH 422-US-005-91

To the best of my knowledge, this study was conducted in accordance with applicable Good Laboratory Practice regulations; there were no deviations from these regulations that impacted on study conclusions.

Study Director

Date